BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/27 — A1

(11) International Publication Number: WO 96/32104

(43) International Publication Date: 17 October 1996 (17.10.96)

(21) International Application Number: PCT/US96/04956

(22) International Filing Date: 11 April 1996 (11.04.96)

(30) Priority Data:

08/420,913	12 April 1995 (12.04.95)	US
60/001,888	4 August 1995 (04.08.95)	US

(71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).

(72) Inventor: CAMDEN, James, Berger; 7339 Charter Cup Lane, West Chester, OH 45069 (US).

(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A PHARMACEUTICAL COMPOSITION CONTAINING N-CHLOROPHENYLCARBAMATES AND N-CHLOROPHENYLTHIOCARBAMATES FOR INHIBITING THE GROWTH OF VIRUSES AND CANCERS

(57) Abstract

This invention is a pharmaceutical composition that inhibits the growth of cancers and tumors in mammals, particularly in human and warm-blooded animals. The composition is also effective against viruses. The composition contains N-chlorophenylcarbamates and N-chlorophenylthiocarbamates which are systemic herbicides. The composition can also contain N-chlorophenylcarbamates and N-chlorophenylthiocarbamates along with a chemotherapeutic agent and optionally a potentiator. A composition for treating viral infections in animals or humans comprising a safe and effective amount of N-chlorophenylcarbamates and the N-chlorophenylthiocarbamates and a potentiator is also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

A PHARMACEUTICAL COMPOSITION CONTAINING N-CHLOROPHENYLCARBAMATES AND N-CHLOROPHENYLTHIOCARBAMATES FOR INHIBITING THE GROWTH OF VIRUSES AND CANCERS

TECHNICAL FIELD

This invention is a pharmaceutical composition that inhibits the growth of cancers and tumors in mammals, particularly in human and warm blooded animals. The composition is also effective against viruses. The composition contains N-chlorophenylcarbamates and N-chlorophenylthiocarbamates which are systemic herbicides. Other composition contains N-chlorophenylcarbamates and N-chlorophenylthiocarbamates along with potentiators or chemotherapeutic agents or antiviral drugs.

BACKGROUND OF THE INVENTION

Cancers are the leading cause of death in animals and humans. The exact cause of cancer is not known, but links between certain activities such as smoking or exposure to carcinogens and the incidence of certain types of cancers and tumors has been shown by a number of researchers.

Many types of chemotherapeutic agents have been shown to be effective against cancers and tumor cells, but not all types of cancers and tumors respond to these agents. Unfortunately, many of these agents also destroy normal cells. The exact mechanism for the action of these chemotherapeutic agents are not always known.

Despite advances in the field of cancer treatment the leading therapies to date are surgery, radiation and chemotherapy. Chemotherapeutic approaches are said to fight cancers that are metastasized or ones that are particularly aggressive. Such cytocidal or cytostatic agents work best on cancers with large growth factors, i.e., ones whose cells are rapidly dividing. To date, hormones, in particular estrogen, progesterone and testosterone, and some antibiotics produced by a variety of microbes, alkylating agents, and anti-metabolites form the bulk of therapies available to oncologists. Ideally cytotoxic agents that have specificity for cancer and tumor cells while not affecting normal cells would be extremely desirable. Unfortunately, none have been found and instead agents which target especially rapidly dividing cells (both tumor and normal) have been used.

Clearly, the development of materials that would target tumor cells due to some unique specificity for them would be a breakthrough. Alternatively, materials that were cytotoxic to tumor cells while exerting mild effects on normal cells would be desirable.

Therefore, it is an object of this invention to provide a pharmaceutical composition that is effective in inhibiting the growth of tumors and cancers in mammals with mild or no effects on normal cells.

More specifically, it is an object of this invention to provide an anti-cancer composition comprising a pharmaceutical carrier and a N-chlorophenylcarbamate or N-chlorophenylthiocarbamate derivative as defined herein, along with a method of treating such cancers.

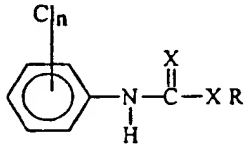
These compositions are also effective against viruses. Therefore it is a further object of this invention to provide a composition effective against HIV, herpes, influenza, rhinoviruses and the like.

It is a further object of this invention to provide a composition effective against HIV, herpes, influenza, rhinoviruses and the like wherein a potentiator is used to improve the effectiveness of the composition.

These and other objects will become evident from the following detailed description of this inventions.

SUMMARY OF THE INVENTION

A pharmaceutical composition for treatment of mammals, and in particular, warm blooded animals and humans, comprising a pharmaceutical carrier and an effective amount anti-cancer compound selected from the group consisting of N-chlorophenylcarbamates and N-chlorophenylthiocarbamates of the formula:



wherein n is from 1 to 3, X is oxygen or sulfur, and R is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenalkyl radicals of up to 8 carbon atoms, and phenyl, and pharmaceutically acceptable inorganic or organic acid salts of these compounds.

These compositions can be used to inhibit the growth of cancers and other malignant tumors in humans or animals by administration of an effective amount of the N-chlorophenylcarbamates and N-chlorophenylthiocarbamates either orally, rectally, topically or parenterally, intravenously, or by direct injection near or into the tumor. These compositions are effective in killing or slowing the growth of tumors, yet are safer than adriamycin on normal, healthy cells. The compositions are also useful for treating viral infections.

The compositions can also be used in combination with potentiators and chemotherapeutic agents.

DETAILED DESCRIPTION OF THE INVENTION

A. DEFINITIONS

As used herein, the term "comprising" means various components can be conjointly employed in the pharmaceutical composition of this invention. Accordingly, the terms "consisting essentially of" and "consisting of" are embodied in the term comprising.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

As used herein, the term "safe and effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the type of mammal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compounds or its derivatives.

As used herein, a "pharmaceutical addition salts" includes a pharmaceutically acceptable salt of the anti-cancer compound. These include organic or inorganic acid salts of the amines. Preferred acid salts are the hydrochlorides, acetates, salicylates, nitrates and phosphates.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the anti-cancer agent to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind.

As used herein, "cancer" refers to all types of cancers or neoplasm or tumors found in mammals.

As used herein, the "anti-cancer compounds" are N-chlorophenylcarbamates and N-chlorophenylthiocarbamates.

As used herein, "viruses" includes viruses which cause diseases (viral infection) in man and other warm blooded animals such as HIV virus, herpes, influenza and rhinoviruses.

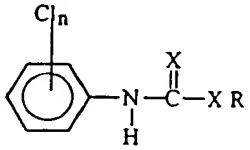
As used herein "potentiators" are materials such as triprolidine and its cis-isomer which are used in combination with N-chlorophenylcarbamates and N-chlorophenylthiocarbamates. Potentiators can affect the immune system or enhance the effectiveness of the drugs.

As used herein "chemotherapeutic agents" includes DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents and others, such as Asparaginase or hydroxyurea.

B. THE ANTI-CANCER COMPOUNDS

The anti-cancer compounds are N-chlorophenylcarbamates and N-chlorophenylthiocarbamates which are known for their herbicidal activities. They are systemic herbicides used to prevent and eradicate certain plants or weeds. Systemic herbicides are differentiated from other herbicides by their ability to be absorbed by the plant and to move through the plant. This systemic ability is not a necessary requirement of the compounds of this invention.

The compounds have the following structure



wherein n is from 1 to 3, X is oxygen or sulfur and R is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenalkyl of up to 8 carbon atoms and phenyl, and the pharmaceutically acceptable salts of these compounds.

Preferred compounds are those in which R is alkyl with 1 to 4 carbons, preferably, isopropyl and X is oxygen, n is 1 and the chloro group is in the 3 position on the phenyl group. N-3-chlorophenylcarbamate is a most preferred compound.

These compounds are prepared according to the method described in U.S. 2,695,225 issued to Witman (1954) and U.S. 2,734,911 issued to Strain (1956).

C. CHEMOTHERAPEUTIC AGENTS

The chemotherapeutic agents are generally grouped as DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents and others such as Asparaginase or hydroxyurea. Each of the groups of chemotherapeutic agents can be further divided by type of activity or compound. The chemotherapeutic agents used in combination with N-chlorophenylcarbamates and N-chlorophenylthiocarbamates include members of all of these groups. For a detailed discussion of the chemotherapeutic agents and their method of administration, see Dorr, et al, *Cancer Chemotherapy Handbook*, 2d edition, pages 15-34, Appleton & Lange (Connecticut, 1994) herein incorporated by reference.

DNA-Interactive Agents include the alkylating agents, e.g. Cisplatin, Cyclophosphamide, Altretamine; the DNA strand-breakage agents, such as Bleomycin; the intercalating topoisomerase II inhibitors, e.g., Dactinomycin and Doxorubicin); the nonintercalating topoisomerase II inhibitors such as, Etoposide and Teniposde; and the DNA minor groove binder Plicamydin.

The alkylating agents form covalent chemical adducts with cellular DNA, RNA, and protein molecules and with smaller amino acids, glutathione and similar chemicals. Generally,

these alkylating agents react with a nucleophilic atom in a cellular constituent, such as an amino, carboxyl, phosphate, sulfhydryl group in nucleic acids, proteins, amino acids, or glutathione. The mechanism and the role of these alkylating agents in cancer therapy is not well understood. Typical alkylating agents include:

Nitrogen mustards, such as Chlorambucil, Cyclophosphamide, Isofamide, Mechlorethamine, Melphalan, Uracil mustard;

Aziridine such as Thiotepa

methanesulphonate esters such as Busulfan;

nitroso ureas, such as Carmustine, Lomustine, Streptozocin;

platinum complexes, such as Cisplatin, Carboplatin;

bioreductive alkylator, such as Mitomycin, and Procarbazine, Dacarbazine and Altretamine;

DNA strand breaking agents include Bleomycin;

DNA topoisomerase II inhibitors include the following:

Intercalators, such as Amsacrine, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, and Mitoxantrone;

nonintercalators, such as Etoposide and Teniposide.

The DNA minor groove binder is Plicamycin.

The antimetabolites interfere with the production of nucleic acids by one or the other of two major mechanisms. Some of the drugs inhibit production of the deoxyribonucleoside triphosphates that are the immediate precursors for DNA synthesis, thus inhibiting DNA replication. Some of the compounds are sufficiently like purines or pyrimidines to be able to substitute for them in the anabolic nucleotide pathways. These analogs can then be substituted into the DNA and RNA instead of their normal counterparts. The antimetabolites useful herein include:

folate antagonists such as Methotrexate and trimetrexate

pyrimidine antagonists, such as Fluorouracil, Fluorodeoxyuridine, CB3717, Azacitidine, Cytarabine, and Floxuridine

purine antagonists include Mercaptopurine, 6-Thioguanine, Fludarabine, Pentostatin;

sugar modified analogs include Cyctrabine, Fludarabine;

ribonucleotide reductase inhibitors include hydroxyurea.

Tubulin Interactive agents act by binding to specific sites on tubulin, a protein that polymerizes to form cellular microtubules. Microtubules are critical cell structure units. When the interactive agents bind on the protein, the cell can not form microtubules Tubulin Interactive agents include Vincristine and Vinblastine, both alkaloids and Paclitaxel.

Hormonal agents are also useful in the treatment of cancers and tumors. They are used in hormonally susceptible tumors and are usually derived from natural sources. These include:

estrogens, conjugated estrogens and Ethinyl Estradiol and Diethylstilbesterol, Chlortrianisen and Idenestrol;

progestins such as Hydroxyprogesterone caproate, Medroxyprogesterone, and Megestrol;

androgens such as testosterone, testosterone propionate; fluoxymesterone, methyltestosterone;

Adrenal corticosteroids are derived from natural adrenal cortisol or hydrocortisone. They are used because of their anti inflammatory benefits as well as the ability of some to inhibit mitotic divisions and to halt DNA synthesis. These compounds include, Prednisone, Dexamethasone, Methylprednisolone, and Prednisolone.

Leutinizing hormone releasing hormone agents or gonadotropin-releasing hormone antagonists are used primarily the treatment of prostate cancer. These include leuprolide acetate and goserelin acetate. They prevent the biosynthesis of steroids in the testes.

Antihormonal antigens include:

antiestrogenic agents such as Tamosifen,

antiandrogen agents such as Flutamide ; and

antiadrenal agents such as Mitotane and Aminoglutethimide.

Hydroxyurea appears to act primarily through inhibition of the enzyme ribonucleotide reductase.

Asparaginase is an enzyme which converts asparagine to nonfunctional aspartic acid and thus blocks protein synthesis in the tumor.

Taxol is a preferred chemotherapeutic agent.

D. POTENTIATORS

The "potentiators" can be any material which improves or increase the efficacy of the pharmaceutical composition or acts on the immune system. One such potentiator is triprolidine and its cis-isomer which are used in combination with the chemotherapeutic agents and the N-chlorophenylcarbamates and N-chlorophenylthiocarbamates. Triprolidine is described in US 5,114,951 (1992). Another potentiator is procodazole, 1H-Benzimidazole-2-propanoic acid; [ß-(2-benzimidazole) propionic acid; 2-(2-carboxyethyl)benzimidazole; propazol]. Procodazole is a non-specific active immunoprotective agent against viral and bacterial infections and can be used with the compositions claimed herein. It is effective with the N-chlorophenylcarbamates and the N-chlorophenylthiocarbamates alone in treating cancers, tumors, leukemia and viral infections or combined with chemotherapeutic agents.

Generally an amount effective to enhance the activity of the pharmaceutical composition is used.

Propionic acid and its salts and esters can also be used in combination with the pharmaceutical compositions claimed herein.

Antioxidant vitamins such as vitamins A, C and E and beta-carotene can be added to these compositions.

E. - DOSAGE

Any suitable dosage may be given in the method of the invention. The type of compound and the carrier and the amount will vary widely depending on the species of the warm blooded animal or human, body weight, and tumor being treated. Generally a dosage of between about 2 milligrams (mg) per kilogram (kg) of body weight and about 400 mg per kg of body weight is suitable. Preferably from 15 mg to about 150 mg/kg of body weight is used. Generally, the dosage in man is lower than for small warm blooded mammals such as mice. A dosage unit may comprise a single compound or mixtures thereof with other compounds or other cancer inhibiting compounds. The dosage unit can also comprise diluents, extenders, carriers and the like. The unit may be in solid or gel form such as pills, tablets, capsules and the like or in liquid form suitable for oral, rectal, topical or parenteral administration or intravenous administration or by injection into or around the tumor site.

The range and ratio of N-chlorophenylcarbamates and the N-chlorophenylthiocarbamates to chemotherapeutic agent will depend on the type of cancer or tumor being treated and the particular chemotherapeutic agent. The amount of chemotherapeutic agent used can be lower than that of the N-chlorophenylcarbamates and the N-chlorophenylthiocarbamates and can range from 0.5 mg/kg body weight to about 400 mg/kg body weight.

F. DOSAGE DELIVERY FORMS

The anti-cancer compounds are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid and the type is generally chosen based on the type of administration being used. The active agent can be coadministered in the form of a tablet or capsule, as an agglomerated powder or in a liquid form. Examples of solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats or oils, alcohols or other organic solvents, including esters, emulsions, elixirs, syrups, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners and melting agents. Oral dosage forms would contain flavorants and coloring agents. Parenteral and intravenous forms would also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in US. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics. Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

G. METHOD OF TREATMENT

The method of treatment can be any suitable method which is effective in the treatment of the particular virus or tumor type that is being treated. Treatment may be oral, rectal, topical, parenteral, intravenous administration or injection into or around the tumor site and the like. The method of applying an effective amount also varies depending on the tumor being treated. It is believed that parenteral treatment by intravenous, subcutaneous, or intramuscular application, formulated with an appropriate carrier, additional cancer inhibiting compound or compounds or diluent to facilitate application will be the preferred method of administering the compounds to warm blooded animals.

The method of treating viral infections may also be by oral, rectal, parenteral, topical or intravenous administration. The actual time and dosage will depend on the type of the virus being treated and the desired blood levels.

The following examples are illustrative and are not meant to be limiting to the invention.

Colon, Breast and Lung Tumor Cells Test

The following cell culture tests were performed to test the toxicity of N-chlorophenylcarbamates and N-chlorophenylthiocarbamates compounds on colon, breast and lung human tumor cells. The viability of the cells were tested by looking at MTT (3-[4,5-dimethylthiazol-2-yl] -2,5-diphenyltetrazolium bromide) reduction. MTT assay is a well known measure of cell viability.

The colon tumor cells (HT29 from American Type Culture Collection (ATCC)) and the breast cells (MX1 from cell lines from ATCC) were cultured in Eagle's Minimal Essential Medium with 10% fetal bovine serum. The lung tumor cells (A549 from ATCC cell lines) were cultured in Ham's F12 medium with 10% fetal bovine serum.

The tumor cells were passaged and seeded into culture flasks at the desired cell densities. The culture medium was decanted and the cell sheets were washed twice with phosphate buffered saline (PBS). The cells were trypsinized and triturated prior to seeding the flasks. Unless otherwise indicated the cultures were incubated at 37 $\pm$ 1° C in a humidified atmosphere of 5$\pm$ 1% carbon dioxide in air. The cultures were incubated until they were 50-80% confluent.

The cells were subcultured when the flasks were subconfluent. The medium was aspirated from the flasks and the cell sheets rinsed twice with PBS. Next, the Trypsin Solution

was added to each flask to cover the cell sheet. The Trypsin Solution was removed after 30-60 seconds and the flasks were incubated at room temperature for two to six minutes. When 90% of the cells became dislodged, growth medium was added. The cells were removed by trituration and transferred to a sterile centrifuge tube. The concentration of cells in the suspension was determined, and an appropriate dilution was made to obtain a density of 5000 cells/ml. The cells were subcultured into the designated wells of the 96-well bioassay plates (200 microliter cell suspension per well). PBS was added to all the remaining wells to maintain humidity. The plates were then incubated overnight before test article treatment.

Each dose of test article was tested by treating quadruplicate wells of cultures with 100 microliter of each dilution. Those wells designated as solvent controls received an additional 100 microliter of methanol control; negative controls wells received an additional 100 microliters of treatment medium. PBS was added to the remaining wells not treated with test article or medium. The plates were then incubated for approximately 5 days.

At the end of the 5 day incubation, each dose group was examined microscopically to assess toxicity. A 0.5 mg/ml dilution of MTT was made in treatment medium, and the dilution was filtered through a 0,.45 micrometer filter to remove undissolved crystals. The medium was decanted from the wells of the bioassay plates. Immediately thereafter, 2000 microliter of the filtered MTT solution was added to all test wells except for the two untreated blank test wells. The two blank wells received 200 microliters of treatment medium. The plates were returned to the incubator for about 3 hours. After incubation, the MTT containing medium was decanted. Excess medium was added to each well and the plates were shaken at room temperature for about 2 hours.

The absorbance at 550 nm (OD_{550}) of each well was measured with a Molecular Devices (Menlo Park, CA) VMax plate reader.

The mean OD_{550} of the solvent control wells and that of each test article dilution, and that of each of the blank wells and the positive control were calculated. The mean OD_{550} of the blank wells was subtracted from the mean of the solvent control wells, and test article wells, respectively to give the corresponding mean OD_{550} .

$$\% \text{ of Control} = \frac{\text{corrected mean } OD_{550} \text{ of Test Article Dilution}}{\text{corrected mean of } OD_{550} \text{ of Solvent Control}} \times 100$$

Dose response curves were prepared as semi-log plots with % of control on the ordinate (linear) and the test article concentration on the abscissa (logarithmic). The EC_{50} was interpolated from the plots for each test article.

For the test articles administered in methanol, separate responses were prepared to correct for the methanol data.

Adriamycin was used as a positive control. In all cases, it was more toxic than any of the test materials by one or two logs. Adriamycin is one of the more potent agents in current use and

one with significant side effects. The peak plasma concentration of other, quite effective chemotherapeutic agents may be 10 to 50 times higher than that of Adriamycin. The EC-50 is the concentration at which one half the cells are killed.

Table 1

Test Material	EC-50 Result (ppm or microgram/ml)					
	HT29	HT29	MX1	MX1	A549	A549
Adriamycin	0.003	0.006	0.02	0.001	0.03	0.009
chloroprofam®	13.3	11.4	91.8	108	12.6	92.5

In normal healthy cells, the following results were obtained:

Table 2

Test Material	EC-50					
	Broncheal Cells		Kerotinovle Cells		Fibroblasts	
chloroprofam®	0.002	>15.2	3.9	13.0	>152	64.2
Adriamycin	0.015	0.0020	0.0035	0.0093	0.065	0.10

These experiments show that these compositions are effective in killing tumor cells without significantly affecting healthy cells.

Other Activity

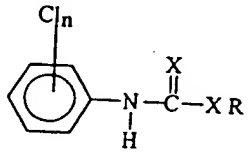
In addition to their combination with chemotherapeutic agents and potentiators, N-chlorophenylcarbamates and the N-chlorophenylthiocarbamates can be combined with fungicides, herbicides or other antiviral agents. Preferred herbicides and fungicides include carbendazim, fluoconazole, benomyl, glyphosate and propicodazole.

The N-chlorophenylcarbamates and N-chlorophenylthiocarbamates are also effective against viruses including rhinovirus, HIV, herpes, and influenza. In the treatment of viral infections, the N-chlorophenylcarbamates and the N-chlorophenylthiocarbamates can be combined with other anti-viral agents to effectively treat viral infections.

It is believed that many herbicides alone or in combination with other herbicides and fungicides will show this beneficial anti-tumor effect.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating viral infections and cancers or tumors comprising a safe and effective amount of N-chlorophenylcarbamates and N-chlorophenylthiocarbamates of the formula:



wherein n is from 1 to 3; X is selected from the group consisting oxygen and sulfur and wherein R is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenyl and phenalkyl of up to 8 carbon atoms and pharmaceutically acceptable inorganic or organic acid salts of these compounds.

2. A pharmaceutical composition according to Claim 1 comprising in addition a safe and effective amount of a chemotherapeutic agent

3. A pharmaceutical composition according to Claim 1 or 2 comprising a pharmaceutically acceptable carrier and a safe and effective amount of N-chlorophenylcarbamates and N-chlorophenylthiocarbamates.

4. A pharmaceutical composition according to Claim 1,2 or 3 wherein R is alkyl of from 1 to 4 carbons, n is 1, X is O and the chloro is in the 3 position of the phenyl.

5. A pharmaceutical composition according to claim 2,3 or 4 wherein said chemotherapeutic agent is selected from the group consisting of DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents, Asparaginase or hydroxyurea.

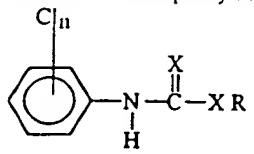
6. A pharmaceutical composition according to claim 5 wherein said chemotherapeutic agent is selected from the group consisting of Asparaginase, hydroxyurea, Cisplatin, Cyclophosphamide, Altretamine, Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposide, Taxol, Plcamydin, Methotrexate, Fluorouracil, Fluorodeoxyuridine, CB3717, Azacitidine, Cytarabine, Floxuridine, Mercaptopurine, 6-Thioguanine, Fludarabine, Pentostatin, Cyctrabine, and Fludarabine.

7. A pharmaceutical composition according to claim 1,2,3,4,5 or 6 which further comprises a potentiator.

8. A method of treating cancer in warm blooded mammals comprising administering from about 2 mg/kg body weight to about 400 mg/kg of a pharmaceutical composition according to claims 1,2,3,4,5,6 or 7.

9. A method according to Claim 8 wherein said N-chlorophenyl carbamate is administered orally, enterically, intravenously, parenterally or by injection into or around the tumor site.

10. A unit dosage composition effective for treating cancers, tumors and viral infections comprising a N-chlorophenylcarbamates and N-chlorophenylthiocarbamates of the formula:



wherein X is selected from the group consisting of oxygen and sulfur, n is from 1 to 3 and R is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenalkyl of up to 8 carbon atoms, phenyl, and the pharmaceutically acceptable organic and inorganic acid salts thereof, and a safe and effective carrier.

11. A unit dosage composition according to Claim 10 wherein said carbamate is N-3-chlorophenylcarbamate and wherein from about 2 mg/kg body weight to about 400 mg/kg of said N-3-chlorophenyl carbamate is administered.

12. A unit dosage composition according to Claim 10 or 11 wherein said pharmaceutically acceptable acid addition salts are selected from the group consisting of and mixtures thereof hydrochlorides, phosphates, nitrates, acetates and salicylates.

13. A unit dosage composition according to Claim 12 further comprising a safe and effective amount of a chemotherapeutic agent.

14. A unit dosage composition according to Claims 10, 11, 12 or 13 wherein said chemotherapeutic agent is selected from the group consisting of DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents, Asparaginase or hydroxyurea.

15. A pharmaceutical composition according to claim 14 wherein said chemotherapeutic agent is selected from the group consisting of Asparaginase, hydroxyurea, Cisplatin, Cyclophosphamide, Altretamine, Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposide, Taxol, Plcamydin, Methotrexate, Fluorouracil, Fluorodeoxyuridine, CB3717, Azacitidine, Cytarabine, Floxuridine, Mercaptopurine, 6-Thioguanine, Fludarabine, Pentostatin, Cyctrabine, and Fludarabine.

16. A unit dosage composition according to Claim 15 wherein from about 2 mg/kg body weight to about 400 mg/kg of said N-3-chlorophenyl carbamate is administered.

17. A unit dosage composition according to claims 11, 12, 13, 14 or 15 further comprising a safe and effective amount of a potentiator.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/04956

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/27

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	CANCER RES., vol. 41, no. 5, 1981, pages 1879-83, XP000579495 ZILKAH ET AL.: "Effect of inhibitors of plant cell division on mammalian tumor cells in vitro" see page 1879 see page 1880, right-hand column, line 11 - line 15 see page 1882, left-hand column, line 13 - right-hand column, line 7 see page 1883, left-hand column, last line - right-hand column, line 5 --- -/--	1-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 1996	05.09.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Gerli, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTE. JATIONAL SEARCH REPORT

tr tional Application No
PCT/US 96/04956

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	PROC.AM.ASSOC.CANCER RES., vol. 22, 1981, page 270 XP002011350 ZILKAH ET AL.: "The effect of plant mitotic inhibitors on mammalian tumor cells" see abstract no.1072 ---	1-17
Y	DATABASE EMBASE ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL DIALOG information services; abstract no. 212600, XP002011351 see abstract & J.CELL BIOL., vol. 61, no. 2, 1974, pages 514-36. BROWN ET AL.: "Microtubule biogenesis and cell shape in Ochromonas. III. Effects of the herbicidal mitotic inhibitor isopropyl N phenylcarbamate on shape and flagellum regeneration" ---	1-17
Y	US,A,5 114 951 (KING) 19 May 1992 cited in the application see claim 1 -----	7,17

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

It stional application No.
PCT/US96/04956

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 8, 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTE. ATIONAL SEARCH REPORT

Information on patent family members

Ir stional Application No
PCT/US 96/04956

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5114951	19-05-92	NONE	

PCT/US96/04956

PATENT COOPERATION TREATY

RECEIVED
JAN - 6 1997

From the INTERNATIONAL BUREAU

PCT

To:

P & G Patent Division
International ITC

REED, T., David
The Procter & Gamble Company
5299 Spring Grove Avenue
Cincinnati, OH 45217
ETATS-UNIS D'AMERIQUE

NOTIFICATION CONCERNING SUBMISSION OF PRIORITY DOCUMENTS

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year)	
18 December 1996 (18.12.96)	
Applicant's or agent's file reference 5637XVJ	**IMPORTANT NOTIFICATION**

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US96/04956	11 April 1996 (11.04.96)	12 April 1995 (12.04.95)

Applicant

THE PROCTER & GAMBLE COMPANY

The applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to the following application(s):

Priority application No:	Priority date:	Priority country:	Date of receipt of priority document:
60/001,888	04 Aug 1995 (04.08.95)	US	11 Apr 1996 (11.04.96)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

F. Gateau

Telephone No.: (41-22) 730.91.11

Form PCT/IB/304 (July 1992)

001335359